IMAGING IN THE ERA OF PRECISION MEDICINE AND RADIOGENOMICS

SOCIETY OF PEDIATRIC RADIOLOGY
VANCOUVER, BRITISH COLUMBIA
MAY 17, 2017

James H Thrall MD
Chairman Emeritus, Department of Radiology
Massachusetts General Hospital
Distinguished Juan M Taveras Professor of Radiology
Harvard Medical School
“I want the country that eliminated polio and mapped the human genome to lead a new era of medicine—one that delivers the right treatment at the right time. …Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes—and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

President Barack Obama, State-of-the-Union speech, Jan 20, 2015

$215 million in proposed budget specifically for precision medicine initiatives
Toward Precision Medicine: Building a Knowledge Network and A new Taxonomy of Disease

National Research Council of the National Academies, White Paper, 2011

“The tailoring of medical treatment to the individual characteristics of each patient”

“Classification of patients into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases, or in response to a specific treatment”

Subpopulations defined by genotype and phenotype
Phenotype

*Phenotype:* Originally taken as “grossly” observable characteristics but now extending to phenomena made observable by technology such as imaging.

ICD 10 (International Classification of Disease) is based almost entirely on disease phenotype, not genotype.

Classification, grading and scoring systems define *sub populations—sub phenotypes* of disease manifestation.
Imaging and Precision Medicine: Terminology

*Imaging Phenotype:* Manifestations of a disease or condition demonstrated by imaging

*Imaging Biomarkers:* Image findings that are linked to the presence, location, extent, severity or behavior of a disease or condition

*Radiology Report* = written description of the imaging phenotype of a disease or condition

*Radiogenomics:* The study of the linkage between genotype and imaging phenotype
COPD imaging phenotypes—bronchiectasis

- Cylindrical (mild)
- Varicose (moderate)
- Cystic (severe)

Courtesy G Abbot, MGH
Bronchiectasis: Cylindrical

Cabochoon ring

Courtesy G Abbot, MGH
Bronchiectasis: Varicose

Courtesy G Abbot, MGH
Bronchiectasis: Cystic

Courtesy G Abbot, MGH
Morphologic (Anatomic) biomarkers
- Presence, size, number, location, shape, texture

Molecular biomarkers
- Molecular target localization (MI), molecular content (MRS), gene expression

Micro environmental biomarkers
- Vasculature, perfusion, diffusion, Ktrans, pH, O2 extraction

Metabolic biomarkers
- Glucose, CMRO2, Protein synthesis

Functional biomarkers
- Organ function—EF, CO, GFR, Cell function, fMRI

The Imaging Biomarker “Toolkit”
The Spot Sign: An Imaging Biomarker in Intra-cerebral Hemorrhage

**Spot Sign**: contrast within the area of hemorrhage on CT angiography indicates active bleeding

**Spot Sign Score**: 0-4

- 1-2 spot signs: 1 point
- $\geq 3$ spot signs: 2 points
- Max axial dimension $\geq 5\text{mm}$: 1 point
- Max attenuation $\geq 180\text{HU}$: 1 point

Javier Romero, MGH
Spot sign score of 3

Courtesy of H Romero, MGH
Expansion

18mL

98mL

Expired

Courtesy of H Romero, MGH
Predictive Value of the Spot Sign Score in 1° ICH

<table>
<thead>
<tr>
<th>Score (n)</th>
<th>Risk of Expansion %</th>
<th>Hospital Mortality %</th>
<th>Mean ICH Expan,mL (range)</th>
<th>Mean ICH Expan,% (range)</th>
<th>Mean IVH Expan,mL (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (362)</td>
<td>2</td>
<td>23</td>
<td>11 (2-19)</td>
<td>39 (10-140)</td>
<td>0 (0-1)</td>
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<tr>
<td>1 (33)</td>
<td>33</td>
<td>42</td>
<td>9 (3-22)</td>
<td>21 (5-38)</td>
<td>1 (0-4)</td>
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<tr>
<td>2 (28)</td>
<td>50</td>
<td>50</td>
<td>9 (3-18)</td>
<td>39 (16-128)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>3 (30)</td>
<td>94</td>
<td>63</td>
<td>21 (5-80)</td>
<td>68 (10-448)</td>
<td>5 (0-48)</td>
</tr>
<tr>
<td>4 (24)</td>
<td>100</td>
<td>71</td>
<td>36 (6-136)</td>
<td>72 (13-293)</td>
<td>12 (0-76)</td>
</tr>
</tbody>
</table>
Clinical Trials Based on The Spot Sign

- **STOP-IT** = spot sign and recombinant factor VIIa, University of Cincinnati

- **SPOT LIGHT** = spot sign and recombinant factor VIIa, Stonybrook

- **ATTACH II+ SCOREIT** = blood pressure management and spot sign positive cases MGH

- **STOP-AUST** = Tranexamic acid and Spot sign, Australia and Asia

- **SPOTSURGE** = surgical trial using spot sign for triage for patients
The Importance of adequate phenotype designation in clinical trials
The Importance of adequate (sub) phenotype designation

- Diagnosis
- Prognosis
- Selection of therapy
- Selection of patients for clinical trials
- Assessment of therapeutic efficacy

Total Patient Population  Sub populations
Response To Therapy As a Phenotype Characteristic

- No response
- Partial Response
- Complete response
- Disease progression

Imaging based treatment response classification systems:
- **RECIST**: Response Evaluation Criteria in Solid Tumors—anatomy
- **PERCIST**: Positron emission tomography response criteria in solid tumors—radiopharmaceutical uptake
- **EORTC**: European Organization for Research and Treatment of Cancer criteria
- **Cheson Criteria**: Lymphoma
FDG PET in Lymphoma

Baseline

April 2012

Disease progression

February 2012

Partial response

December 2011

Baseline

DLBCL progressed after brief response to second line therapy
FDG PET/CT in a Patient with Lymphoma

FDG PET/CT Fusion Images

Initial PET scan

Complete response

F/U PET scan

Initial PET scan
IPS as Predictor of Treatment Response

International Prognostic Score-- IPS

Gallamini et al. JCO, 2007
FDG PET changed the IPS prediction for survival.

"Chemosensitive" by PET

Non Chemosensitive by PET

Gallamini et al. JCO, 2007
**Response-adapted therapy** using PET in patients with early-stage Hodgkin’s lymphoma (Randomized Phase III Trial to Determine the Role of FDG–PET Imaging in Clinical Stages IA/IIA Hodgkin’s Disease [RAPID])

Kaplan–Meier Plot of Overall Survival (OS) in PET negative patients after three rounds of chemotherapy

Rate ratio, 0.51 (95% CI, 0.15–1.68)

P=0.27

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy</th>
<th>No further treatment</th>
</tr>
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<tr>
<td>209</td>
<td>200</td>
<td>191</td>
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<td>196</td>
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<tr>
<td>18</td>
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<td>2</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ADC$_{\text{min}}$ is a Prognostic Biomarker in Ovarian Cancer (ADC—Apparent Diffusion Coefficient)

111 patients with preoperative DWI

CA--125 (Cancer Antigen 125)

Disease free survival rate (%) vs. months

A. CA125 ($\leq 56.63$) (n=94)
B. CA125 ($> 56.63$) (n=17)

P=0.0395*

ECOG—ACRIN
Cancer Research Group

IMAGING AND GENOTYPE/GENE EXPRESSION
Molecularly targeted therapy in cancer: Somatic mutations and gene expression

- Non-small cell lung cancer: EGFR domain—Iressa, Tarceva
  - Positive response
- Melanoma: BRAF--B-raf—Zelboraf
  - Positive response
- Breast cancer--Her 2 neu—Herceptin (Greene 1985)
  - Positive response
- Colon cancer: KRAS—Eribitux, Vectibix
  - Negative response
- GI stromal tumors: brc/abl oncogene—Gleevec
  - Positive response

The Cancer Genome Atlas (TCGA), National Cancer Institute
~100 FDA approved molecularly targeted drugs for 28 cancers
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.


Article cited over 9000 times
Radiogenomics: Discovery of Mutations; Link between Imaging Phenotype and Tissue Genotype

Classic NSCLC Phenotype by histopathology
100%

Treatment with tyrosine kinase inhibitor (Iressa)

Tumors responding to treatment
~10-12%
Radiogenomics: Discovery of Mutations; Link between Imaging Phenotype and Tissue Genotype

Classic NSCLC Phenotype by histopathology 100%

Treatment with tyrosine kinase inhibitor (Iressa)

Tumors responding to treatment ~10-12%

Somatic tissue genotyping of tumors

Tumors with EGFR mutations ~10%

Imaging response phenotype

Discovery of EGFR mutations

ATP cleft within the kinase domain of EGFR
Cancer researchers: It’s time to pay more attention to ‘miracle’ patients

By Erin Blakemore  August 26 at 8:00 AM

Exceptional Responders Initiative: Questions and Answers

Posted: September 24, 2014  Updated: March 23, 2015
NATIONAL CANCER INSTITUTE
NCI-MATCH CLINICAL TRIAL

THIS PRECISION MEDICINE TRIAL EXPLORES TREATING PATIENTS BASED ON THE MOLECULAR PROFILES OF THEIR TUMORS

NCI-MATCH* IS FOR ADULTS WITH:
- solid tumors (including rare tumors) and lymphomas
- tumors that no longer respond to standard treatment

ABOUT 5,000 CANCER PATIENTS WILL BE SCREENED WITH A TUMOR BIOPSY

THE BIOPSIED TUMOR TISSUE WILL UNDERGO GENE SEQUENCING

GENE SEQUENCING WILL LOOK FOR CHANGES IN 143 GENES

IF A PATIENT'S TUMOR HAS A GENETIC ABNORMALITY THAT MATCHES ONE TARGETED BY A DRUG USED IN THE TRIAL, THE PATIENT WILL BE ELIGIBLE TO JOIN THE TREATMENT PORTION OF NCI-MATCH

NOT ALL PATIENTS WILL HAVE TUMORS WITH AN ABNORMALITY THAT MATCHES A DRUG BEING TESTED

PATIENTS WITH TUMORS THAT SHARE THE SAME GENETIC ABNORMALITY, REGARDLESS OF TUMOR TYPE, WILL RECEIVE THE DRUG THAT TARGETS THAT ABNORMALITY

*NCI-Molecular Analysis for Therapy Choice

www.cancer.gov/nci-match
To learn more, call 1-800-4-CANCER

NCI National Clinical Trials Network
Diagnosis and classification of cancer; changing rapidly from organ system based histopathological phenotypes to (molecular) genotypes

- Mutations associated with drug sensitivity
  - EGFR Gly719X, exon 19 deletion, Leu858Arg, Leu861Gln
- Mutations associated with primary drug resistance
  - EGFR exon 20 insertions
- Mutations associated with acquired drug resistance
  - EGFR Thr790Met, Asp761Tyr, Leu747Ser, Thr854Ala

Pao and Girard. Lancet Oncology.
2011;12:175-180
Prostate Cancer
Revealing Heterogeneous Biology of Tumor Metastasis

CT

$^{18}$F-FDG PET/CT
Glycolysis

$^{18}$F-FDHT PET/CT
Androgen Receptor

Hricak H.: Oncologic Imaging: A Guiding Hand of Personalized Cancer Care; Radiology 2011
Prostate Cancer

Revealing Heterogeneous Biology of Tumor Metastasis

Tumor heterogeneity is the key factor limiting response to targeted therapy. Personalized medicine depends on biomarkers for selecting patients and directing therapy.


Zr-89 J591 PSMA mAb*

## MSKCC Molecular Imaging Probe INDs (n = 36)

<table>
<thead>
<tr>
<th>Imaging Agent</th>
<th>Imaging Target</th>
<th>Cancer Site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small Molecules (Imaging)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>tumor metabolism</td>
<td>Recurrent prostate cancer</td>
</tr>
<tr>
<td>$[^{18}]$F-FLT</td>
<td>tumor cell proliferation</td>
<td>Lymphoma, prostate, H&amp;N, NSCLC</td>
</tr>
<tr>
<td>$[^{18}]$F-FES</td>
<td>estrogen receptor status</td>
<td>Breast</td>
</tr>
<tr>
<td>$[^{18}]$F-FDHT</td>
<td>androgen receptor</td>
<td>Prostate</td>
</tr>
<tr>
<td>$[^{18}]$F-FMISO</td>
<td>tumor oxygenation</td>
<td>Head &amp; Neck, Rectal</td>
</tr>
<tr>
<td>$[^{18}]$F-FACBC</td>
<td>amino acid metabolism</td>
<td>Breast, Prostate, Brain</td>
</tr>
<tr>
<td>$[^{18}]$F-dasatinib</td>
<td>tyrosine kinases</td>
<td>Prostate, Breast</td>
</tr>
<tr>
<td>$[^{18}]$F-glutamine</td>
<td>tumor metabolism</td>
<td>All solid malignancies</td>
</tr>
<tr>
<td>$[^{18}]$F-choline</td>
<td>cellular membrane phospholipids</td>
<td>Brain</td>
</tr>
<tr>
<td>$[^{18}]$F-MFBG</td>
<td>NET-expressing tumor</td>
<td>Pediatric and Adult Neuroendocrine Malignancies</td>
</tr>
<tr>
<td>$[^{124}]$I-PUH71* (theranostic)</td>
<td>HSP-90</td>
<td>All solid malignancies and lymphoma (with PUH71 therapy)</td>
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<tr>
<td><strong>Peptides (Imaging)</strong></td>
<td></td>
<td></td>
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<tr>
<td>$^{68}$Ga-DOTA-RM2</td>
<td>GRPr-positive tumors (bombesin)</td>
<td>Prostate</td>
</tr>
<tr>
<td>$[^{124}]$I-3F8</td>
<td>disialoganglioside GD2</td>
<td>Neuroblastoma (pediatrics)</td>
</tr>
<tr>
<td>$[^{124}]$I-8H9</td>
<td>8H9 antigen</td>
<td>Multiple tumors e.g. Leptomeninges (pediatrics)</td>
</tr>
<tr>
<td>$[^{89}]$Zr-DFO-huJ591</td>
<td>PSMA</td>
<td>Prostate, Brain</td>
</tr>
<tr>
<td>$[^{89}]$Zr-DFO-Trastuzumab</td>
<td>HER2</td>
<td>Breast, Gastric</td>
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<tr>
<td>$[^{89}]$Zr-DFO-MSTP2109A</td>
<td>PSMA</td>
<td>Prostate</td>
</tr>
<tr>
<td>$[^{89}]$Zr-DI-IAB2M</td>
<td>PSMA</td>
<td>Prostate</td>
</tr>
<tr>
<td><strong>Antibodies and Fragments (Therapy)</strong></td>
<td></td>
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<tr>
<td>$^{131}$I-8H9</td>
<td>8H9 antigen</td>
<td>Multiple tumors e.g. Leptomeninges (pediatrics)</td>
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<tr>
<td>$[^{124}]$I-3F8</td>
<td>disialoganglioside GD2</td>
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<tr>
<td>$[^{124}]$I-hu3F8</td>
<td>disialoganglioside GD2</td>
<td>Neuroblastoma (pediatrics)</td>
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<tr>
<td><strong>Nanoparticles (Imaging)</strong></td>
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<tr>
<td>$[^{124}]$I-Cdot nanoparticles</td>
<td>Avβ3</td>
<td>Melanoma</td>
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<tr>
<td><strong>Hyperpolarized Agents</strong></td>
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</tr>
<tr>
<td>$^{13}$C-pyruvate</td>
<td>Cancer metabolism</td>
<td>Prostate and other solid tumors</td>
</tr>
</tbody>
</table>

**IND Enabling Stage:** $^{68}$Ga/$^{177}$Lu-DOTA-JR11; $[^{89}]$Zr-DFO-trastuzumab; $[^{89}]$Zr-DFO-5B1; $[^{89}]$Zr-DFO-MLYE44789A, $^{131}$I-hu3F8, $^{68}$Ga-pkfz-PSMA

$^{11}$C agents (2015): acetate, thymidine, glucose, martinostat

Completed Studies (n = 11): $[^{18}]$F-FIAU (gene expression), $[^{18}]$F-ML10 (apoptosis), $[^{64}]$Cu-ATSM (hypoxia), $[^{124}]$I-AZGP (hypoxia), $[^{89}]$Ga-Her2 F(ab') (HER2), $^{64}$Cu-DOTA-trastuzumab (HER2), $[^{124}]$I-A33, $[^{124}]$I-G250 (CA9 antigen), $^{111}$In-DOTA-cG250 (CA9 antigen), $^{90}$Y-DOTA-cG250 (CA9 antigen), $^{225}$Ac-lintuzumab (anti-CD33)

Courtesy of H Hricak, MSKCC
Germline Mutations: Imaging for surveillance of occurrence, location, extent, severity

- Monogenic disorders -- >50
  - Cystic fibrosis
  - Huntington’s Disease
  - Neurofibromatosis: NF1, NF2
  - ...
- Polygenic disorders -- TNTC
  - Alzheimer’s Disease
  - Diabetes
  - ...
- Cancer genes
  - BRAC1, 2 – breast and ovarian cancer
  - APC— adenomatous polyposis coli
  - MEN1,2 – multiple endocrine neoplasia
  - ...
The story of her decision to have bilateral mastectomies

• BRCA1 mutation
Story of her decision to have bilateral salpingo-oophorectomies

- 87% risk of breast cancer
- 50% risk of ovarian cancer
- Deleterious variant
- Non-deleterious variant
- Variant of unknown significance
BRCA 1 Positive

MLO views
T1 fat-saturated gadolinium enhanced MRI with kinetic overlay
Neurofibromatosis 1

Genotype is known–

Imaging used for surveillance of disease manifestations:

Has the disease become manifest?
Where?
How extensive?
Change over time?

Whole body MRI with image segmentation

Courtesy of WL Cai, MGH
Precision Medicine

Observations
Imaging and Precision Medicine

- Assessment of disease prognosis
- Selection of therapy and disease management
- Inclusion criteria for clinical trials
- Assessment of response to therapy— anatomic, metabolic
  - Adaptive therapy
- Definition of “enriched” populations for genetic analysis
- Surveillance of disease manifestation— presence, location, extent and severity
  - Classification and staging
Genome and inherited epigenome

* All inherited factors

Exposome

* Environmental and behavioral factors, microbiome, acquired epigenome

Randomness

Stochastic nature of biological and chemical processes

Expression of gene products

Proteins, lipids, metabolites ("Omic" - proteomics, lipidomics, metabolomics)

Phenome

All the characteristics of an individual—dynamic over time

Interrogation of the phenome

Clinical exam, lab tests, pathology, imaging

Clinical phenotype

Dominant current basis of disease classification and medical practice—ICD 10